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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/415,795	ZHOU ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39,46-49 and 61-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 39, 46-49 and 61-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 18, 2005 amending the specification to correct clerical errors, amending claims 36, 61, 64 and 65 and canceling claims 41-43, 57-60 and 66-70 has been entered.

Claims 36, 39, 46-49 and 61-65 are pending.

Claim Objections

Applicant is advised that should claim 63 be found allowable, claim 64 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Both claims depend from claim 62 and both claims limit "the mammalian cell" or "the cell", respectively, to a human cell.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 39, 46-49 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 36, 39, 46-49 and 61-64 recite an F-box consisting of amino acid residues 148-192 of SEQ ID NO:4 or a "functional homolog or portion thereof". Claim 65 recites "a peptide that is encoded by the nucleotide sequence of SEQ ID NO:3 or functional homolog thereof". The term 'functional analog" is defined in the specification as "functional in a sense that it has the specific biological activity required for the particular subunit, i.e., capability to form an E3 complex" (page 27, lines 11-13). The genus of functional homologs encompasses proteins of diverse structure characterized by function only.

This recitation of the genus fails to provide a sufficient description of the claimed genus of proteins as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. It does not provide an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the proteins that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. The functional definition of the genus does not provide any structural information commonly possessed by members of the genus, which distinguish the protein species within the genus from

other proteins such that one can visualize or recognize the identity of the members of the genus or subgenus.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 36, 39, 46-49 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for targeting a target polypeptides using a hybrid polypeptide comprising F-box protein of SEQ ID NO:4 or its fragment consisting of residues 148-192 of SEQ ID NO:4 and a target polypeptide interaction domain in human cells, does not reasonably provide enablement for a method of use of said hybrid polypeptide in any eukaryotic cell or its functional homolog having no known identity to residues 148-192 of SEQ ID NO:2 in any eukaryotic cell, including human cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claims 36, 39, 46-49 and 61-65 are drawn to a method of use of a hybrid polypeptide comprising F-box protein consisting of residues 148-192 of SEQ ID NO:4 or F-box protein of SEQ ID NO:4 or a functional homolog thereof and a target polypeptide interaction domain in any eukaryotic host cell "wherein the F-box recruits the hybrid polypeptide to a Skp1/Cul1/F-box protein (SCF) ubiquitin ligase complex".

The specification teaches a method of use of a hybrid polypeptide comprising a human F-box protein, βTrCP (SEQ ID NO:4), fused with E7N for degrading the endogenous protein, p107, that is a human pRB analog, when expressed in human C33A cells (pages 138-139, Figure 11, page 140). Therefore, the specification teaches a method of use of a human F-box protein, βTrCP, fused to a known target polypeptide interaction domain, for degrading of a known target polypeptide in human cells.

The art teaches that "F-box proteins directly contact ubiquitination substrates and can display selectivity in recognition of potential targets for ubiquitination, as would be expected of E3 proteins" (Skowyra et al., form PTO-1449 mailed November 14, 2000, reference AF, page 215, 2nd column). The post-filing references disclose the use of

human βTrCP for degradation of proteins in human cells (Remarks of 1/18/05, page 9, last paragraph, through page 10).

Thus, the enablement of the claimed methods depends on the ability of F-box protein to form SCF complex. Such ability of a human F-box protein is demonstrated in human cells, which naturally comprise other requisite protein components of the SCF complex. The ability to form an SCF complex depends on the structure of an F-box protein. A functional homolog thereof having no known identity to residues 148-192 of SEQ ID NO:4 will not form SCF complex. For the same reason F-box protein of SEQ ID NO:4 or consisting of residues 148-192 of SEQ ID NO:4 will not form an SCF complex with "SC" counterparts in any eukaryotic cells. The compositions of SCF ubiquitin ligase complexes are not yet elucidated in most eukaryotic cells. However, the requisite protein components of an SCF complex are not expected to have degree of identity to their human counterparts that is sufficient to form an SCF complex with a human F-box protein of SEQ ID NO:4 or consisting of residues 148-192 of SEQ ID NO:4.

Therefore, one of ordinary skill in the art would require guidance beyond that provided, in order to degrade a target polypeptide by using a hybrid polypeptide comprising an F-box protein of SEQ ID NO:4 or consisting of residues 148-192 of SEQ ID NO:4 in eukaryotic cells other than human cells or by using a functional homolog thereof in any eukaryotic cell, including human cell, in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 36, 39, 46-49 and 61-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36, with dependent claims 39, 46-49 and 61-64, recites a hybrid polypeptide comprising "F-box consisting of an amino acid sequence that is encoded by the nucleotide sequence in SEQ ID NO:3 that encodes amino acids 148-192 of SEQ ID NO:4". Such recitation is confusing because the limitations introduced by reciting the nucleotide sequence are not apparent.

Claim 49 recites "the target polypeptide is selected from the group consisting of a retinoblastoma polypeptide, a p107 polypeptide, IκB, Sic1p, Cln2p, E2 or beta-catenin". Applicants argue that "Each of the recited terms refer to known proteins, such that one of ordinary skill in the art would know how to determine the sequence of each protein using GenBank or another protein database" (Remarks of 1/18/05, page 12). While some polypeptides such as IκB or β-catenin can be found in Registry or GenBank database, for example, others can not. Thus, it is unclear which polypeptide sequences are encompassed by the recited terms. Further, it is unclear why some polypeptides contain "p" while others such as IκB, E2 or β-catenin do not.

Claim 61 is drawn to "The method of claim 36, further comprising a WD domain". Since a "WD domain" is a product not a method, claim 61 is confusing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 36, 39, 46-49, 61 and 65 are rejected under 35 U.S.C. 102(a) as being anticipated by Kumar et al.

Kumar et al. (PNAS (March 1998), 95, 2417-2422, cited on form PTO-892 mailed July 14, 2004) teach that "F-boxes operate independently of WD-repeats " (page 2417, 2nd column). They teach chimeric polypeptides wherein F-box of SCON2 proteins were replaced with foreign F-box containing proteins such as Cdc4p and Met30p expressed in fungus *Neurospora*. Kumar et al. teach that "the ability of these swapped domains to at least partially function within SCON2 suggests a common underlying mechanism of action, possibly involving F-box-mediated proteolysis" (page 2421, 1st column, penultimate paragraph). They further teach that "our findings establish a significance for the F-box motif, with its putative role in targeting substrate proteins for proteolysis, beyond the bounds of cell cycle processes" (page 2417, 2nd column, 2nd paragraph). Thus, Kumar et al. teach a method of targeting a polypeptide comprising F-box and a target interaction domain for proteolysis in a eukaryotic cell.

Absent structural limitations, F-box containing proteins, Cdc4p and Met30p, are construed as functional homologs of an F-box protein consisting of residues 148-192 of SEQ ID NO:4 or a peptide encoded by SEQ ID NO:3.

Response to Arguments

Applicant's arguments filed January 18, 2005 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, written description rejection, the focus of the current rejection is on a functional homolog of a hybrid polypeptide defined by function only that was introduced by the amendment.

With regard to the 112, 1st paragraph, enablement rejection, Applicants argue that "the specification describes that F-boxes from different proteins are high conserved and thus have a similar structure. Given the high conservation, an F-box from one protein from one eukaryotic species is believed to target proteins for degradation in cells of the same eukaryotic species, as well as cells from other eukaryotic species " (Remarks, page 9). This is not agreed with because even if the degree of identity were high, which is not shown, the binding of one F-box protein to form SCF complex does not mean that another F-box protein with an unknown degree of identity would be able to form the SCF complex. For the same reason, F-box protein of SEQ ID NO:4 or a fragment thereof consisting of residues 148-192 would not form SCF complex in other eukaryotic cell unless the proteins that constitute said SCF complex are structurally highly identical to their counterparts in human cells.

Applicants further discuss various post-filing publications (pages 9-10). These arguments are not persuasive because these publications disclose the use of βTrCP in human cells and not in other eukaryotic cells. The use of βTrCP in human cells is enabled.

With regard to the 112, 2nd paragraph, rejection, the relevant part of Applicants' arguments reads "Claim 49 was rejected as allegedly unclear as to which sequences are encompassed by the recited terms. Applicants respectfully traverse the rejection. Each of the recited terms refer to known proteins, such that one of ordinary skill in the art would know how to determine the sequence of each protein using GenBank or another protein database. Further, the recited terms are exemplary sequences that may be targeted using the invention" (page 12). As stated above, the word search of the terms recited in claim 49 in the Registry and GenBank databases revealed information related to only IκB and β-catenin.

With regard to the 102(a) rejection over Kumar et al., Applicants argue that "Kumar et al. does not teach that SCON2 functions through a proteolytic process" (page 13). This is not persuasive for the reasons discussed above. Further, Kumar et al. teach the claimed method, i.e. a method comprising a step of providing a eukaryotic cell comprising a hybrid polypeptide comprising F-box protein and a target interaction domain. Applicants further argue that "Kumar et al. not teach any of the claim limitations of the instant application. In particular, Kumar et al. do not teach human βTrCP or SEQ ID NO:4, which are the subject of the instant application" (page 13). It is agreed that the Kumar et al. article does not anticipate a method of use of a cell comprising a hybrid

polypeptide comprising SEQ ID NO:4 or a fragment thereof consisting of residues 148-192. However, the instant claims are drawn to a method of use a functional homolog thereof. Cdc4p and Met30p are functional homologs of βTrCP (specification, page 30).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

April 22, 2005